Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Lead Evaluation for Defibrillation and Reliability in Left Bundle Branch Area Pacing (LEADR LBBAP)
Clinical Investigation Plan Identifier	MDT22048
Clinical Investigation Plan Version	2.0
Statistical Analysis Plan Version Date	2024NOV04
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted], Senior Statistician [redacted], Senior Principal Statistician
2.0	• Corrected version of Clinical Investigation Plan listed on page 1	[redacted], Senior Statistician [redacted], Senior Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
CCS	Clinical Composite Score
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
(e)CRF	electronic Case Report Form
CRT(-D)	Cardiac Resynchronization Therapy Defibrillator
DMC	Data Monitoring Committee
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
KCCQ	Kansas City Cardiomyopathy Questionnaire
LEADR LBBAP	Lead Evaluation for Defibrillation and Reliability in Left Bundle Branch Area Pacing
LBB(A)P	Left Bundle Branch (Area) Pacing
LOT-CRT	Left Bundle Branch-Optimized Cardiac Resynchronization Therapy
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV(i)	Left Ventricular End Systolic Volume (indexed)
MedDRA	Medical Dictionary for Regulatory Activities
PHD	Pre-Hospital Discharge
RA	Right Atrial
RV	Right Ventricular
RVCM	Right Ventricular Capture Management
SAP	Statistical Analysis Plan
SSVA	Sustained Shockable Ventricular Arrhythmia
VF	Ventricular Fibrillation

3. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to document, before data are analyzed, the study design rationale for the Lead Evaluation for Defibrillation and Reliability in Left Bundle Branch Area Pacing (LEADR LBBAP) Study, and the methods used to analyze the study's objectives, and the planned analyses that will be included in planned study reports. This SAP does not limit the analyses in reports, additional analysis of study data beyond this plan may be needed. Additional analysis for publications or for internal research may not be included in this plan.

LEADR LBBAP is a prospective, pre-market, pivotal, non-randomized, multi-site, interventional, global study. Its purpose is to confirm the safety and defibrillation efficacy of the Next Generation ICD Lead when placed in the LBBAP location in an ICD or LOT-CRT patient population.

The SAP may not be updated in an event of CIP updates if the statistical analysis will not be affected.

This SAP was developed in accordance with the LEADR LBBAP Clinical Investigation Plan (CIP), version 2. Section 3 of the CIP provides a detailed background of the study.

4. Study Objectives

4.1. Primary Objectives

4.1.1 Primary Efficacy Objective

Demonstrate the percentage of patients successfully defibrillated at implant with the Next Generation ICD Lead when placed in the LBBAP location exceeds a pre-specified threshold of 88%.

Endpoint Definition

Successful implant defibrillation is defined as:

- First induced SSVA episode successfully terminated with an 18J or maximum output minus 10 Joule (M-10J) shock, or
- First therapy of the second induced SSVA episode successfully terminated with a M-10J shock, or
- First therapy after a system reposition of an induced SSVA episode successfully terminated with a M-10J shock, or
- Two consecutively induced SSVA episodes successfully terminated with a M-10J shock.

Rationale

While defibrillation testing may not be common practice in all geographies, termination of induced ventricular arrhythmias provides a measure of anticipated device performance in an ambulatory setting, and in this trial at least the first 160 consecutive subjects will undergo defibrillation testing to demonstrate the performance of the lead in terminating ventricular arrhythmias exceeds a pre-specified threshold. The endpoint definition allows for termination of one episode at 18J or M-10J to be tested first to reduce the number of ventricular arrhythmias and device shocks which the subject may experience during testing. Following the same rationale this definition allows termination of the first episode after a system reposition at M-10J.

4.1.2 Primary Safety Objective

Estimate the Next Generation ICD Lead-related major complication rate at 3-months post implant when the Next Generation ICD Lead implant is attempted in the LBBAP location.

Endpoint definition

For an adverse event (AE) to meet the endpoint, defined as a subject's first occurrence of a major complication related to the Next Generation ICD Lead, as determined by an independent Clinical Events Committee (CEC), the event must have occurred within 90 days (inclusive) of the Next Generation ICD Lead implant attempt and be adjudicated by the CEC as being a major complication related (causal relationship) to the Next Generation ICD Lead. Major complications are those complications resulting in:

- Death

- Hospitalization (in-patient)
- Lead Fracture
- Prolongation of an existing hospitalization by at least 48 hours
- System Revision (reposition, replacement, explant)

Rationale

This composite endpoint was chosen to encompass AEs related to the Next Generation ICD lead which requires invasive intervention (leading to the AEs being classified as a complication, see section Section 11.4 of the CIP) as well as serious outcome (in-patient hospitalization, prolongation of an existing hospitalization by at least 48 hours, system revision, death). The majority of Next Generation ICD Lead related complications occur within 3-months of implant attempt. Additionally, electrical performance of cardiac implantable electrical devices is stable within 3-months post-implant.

4.2

[redacted]

5. Investigation Plan

The LEADR LBBAP study is expected to be conducted at up to 40 study sites. Participating geographies may include but are not limited to: Australia, Mainland China, Japan, Hong Kong, Malaysia, Europe, Middle East, and Africa (EMEA), Canada, and the United States. Approximately 300 subjects, including a minimum of 150 LOT-CRT implant attempts (no minimum requirement for ICD implant attempts), will be enrolled.

Subjects will be considered enrolled into the study upon signing the Informed Consent Form (ICF) and will be followed prospectively from consent to implant, 3-months post-implant, 6-months post-implant,

and at subsequent 6-month intervals until study closure. Enrolled subjects will be followed until at least 3-months post-implant (ICD-indicated subjects) or 6-months post-implant (CRT-indicated subjects). Enrollment should not exceed 10% (i.e., 30 subjects if 300 subjects are enrolled) of the final sample size at any individual site. The per-study site enrollment cap may be increased upon Sponsor approval. Figure 1 provides an overview of the LEADR LBBAP study.

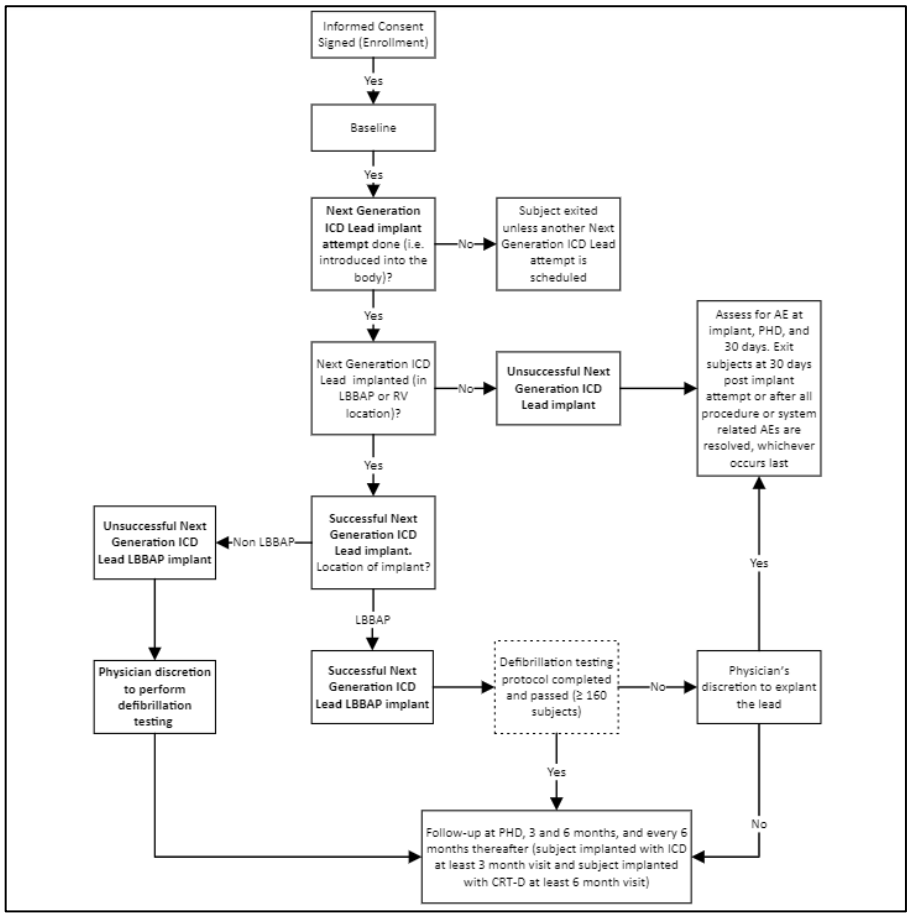


Figure 1: Overview of the LEADR LBBAP Study

Because all subjects are intended to have the Next Generation ICD Lead implanted in the LBBAP position, the study is not designed to provide comparisons between the LBBAP location and any non-LBBAP RV location. In addition, since CRT-D indicated subjects are intended to also undergo LV lead implant, the study is not designed to provide comparison between LOT-CRT and dual-chamber LBBAP. See Section 5 of the CIP for a detailed description of the study design, including duration, rationale, and oversight.

6. Determination of Sample Size

There are two primary objectives (safety and efficacy). The safety primary objective sample size requirement will refer to the number of subjects who undergo an implant attempt of the Next

Generation ICD Lead in the LBBAP location, while the efficacy primary objective samples size will be defined as subjects with the lead successfully implanted in the LBBAP location who complete the implant defibrillation testing protocol.

6.1 Safety Objective Sample Size Determination

The primary safety objective is to estimate the Next Generation ICD Lead-related major complication-free rate at 3 months. The sample size for this objective is not driven by formal hypothesis testing. Rather, it is sized to allow the complication-free rate to be estimated within a desired level of precision. Table 1 provides summaries of the expected confidence interval width and absolute error for these estimates at a variety of sample sizes. The summaries are Monte Carlo approximations based on 10,000 simulations for each sample size. Complications were simulated by an R program using a piecewise exponential distribution where the assumed complication-free rate (shown in Figure 2) was 95.5% at one month and 95.0% at three months. Attrition was simulated using a Weibull distribution where the assumed attrition rate was 4% at one month and 6% at three months.

In over 80% of the simulated samples containing 150 subjects undergoing an LBBAP implant attempt, the confidence interval for the complication-free rate at 3 months was less than 10% wide and the absolute error (the distance from the point estimate to the true value of 95%) was less than 2.5%. Therefore, a sample of at least 150 subjects will be used for this objective.

Table 1: Summary of estimation performance for LBBAP-related major complication-free rate at 3 months.

Number of subjects undergoing LBBAP implant attempts	Median confidence interval width	20th percentile confidence interval width	80th percentile confidence interval width	Median absolute error	20th percentile absolute error	80th percentile absolute error
100	8.67%	6.46%	10.08%	1.32%	0.78%	2.94%
150	6.98%	5.92%	7.98%	1.2%	0.46%	2.27%
200	6.08%	5.25%	6.82%	1.09%	0.37%	1.93%
250	5.45%	4.79%	6.05%	0.88%	0.38%	1.71%

R program: S:/clinicalstudies/CRM/leadr_lbbap/Sample_Size/leadr_lbbap_sample_size_cip_safety.R

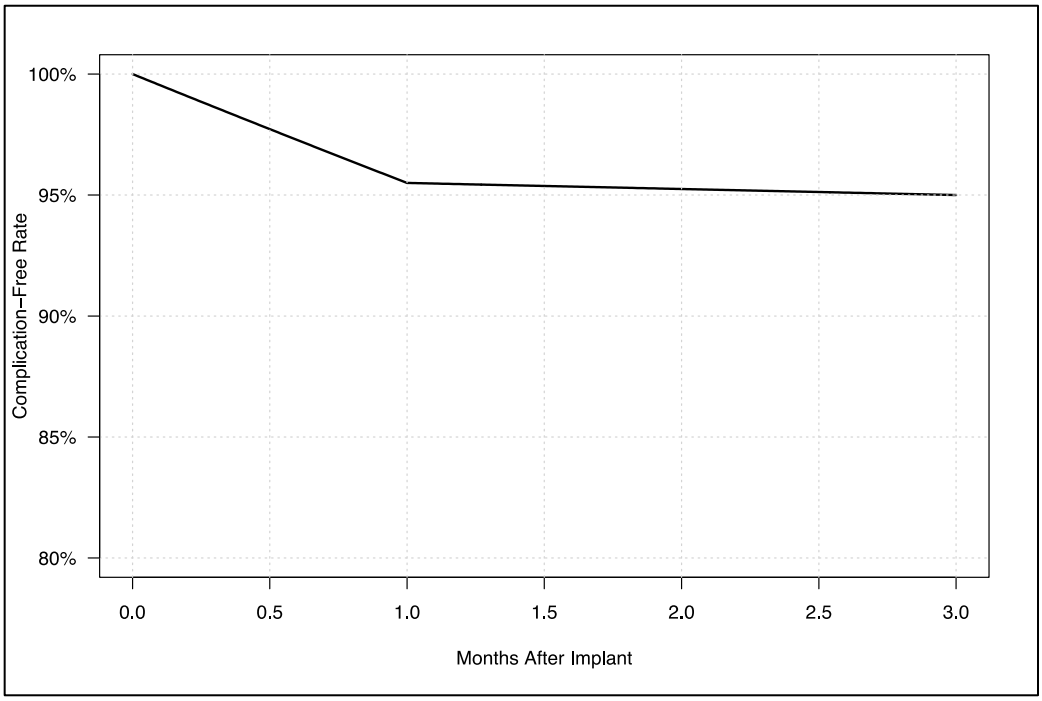


Figure 2. Assumed rate for LBBAP lead-related major complications using the Next Generation defibrillation lead. R program: S:/clinicalstudies/CRM/leadr_lbbap/Sample_Size/leadr_lbbap_sample_size_cip_safety.R

6.2 Efficacy Objective Sample Size Determination

A performance goal of 88% was chosen to evaluate the primary efficacy objective metric of implant testing success defined as successfully terminating one or more induced SSVA episodes. Each subject included in the efficacy objective analysis will be counted as a success or failure. Figure 3 shows the relationship between sample size and statistical power to pass the objective. An R program calculated Monte Carlo power approximations based on 10,000 simulations for each approximation. The assumed true defibrillation success rate is either 97.0% or 95.5%. Defibrillation success samples were generated from a Binomial distribution.

As can be seen in Figure 3, statistical power does not increase monotonically as sample size increases. However, a sample size of at least 160 subjects undergoing defibrillation testing will provide at minimum 90.4% power assuming the true success rate is 95.5% (this minimum occurs with a sample of 170 subjects). Therefore, a sample size of at least 160 subjects will be used for this objective.

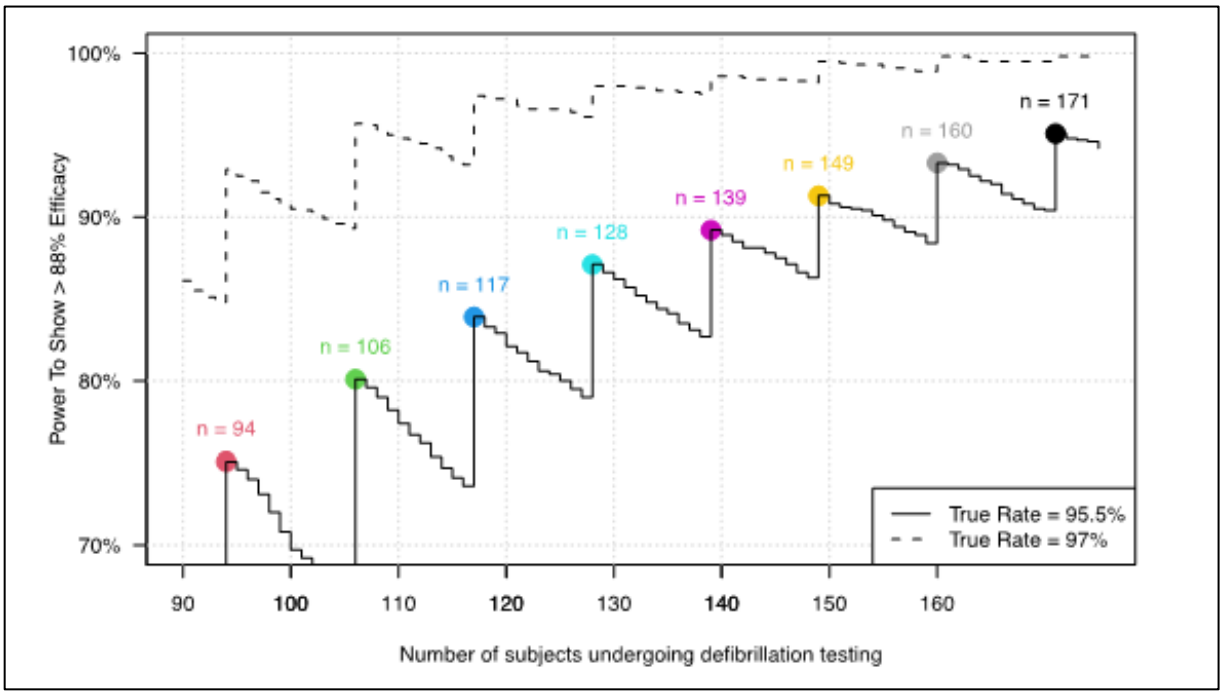


Figure 3. Assumed rate for LBBAP lead-related major complications using the Next Generation defibrillation lead. R program: S:/clinicalstudies/CRM/leadr_lbbap/Sample_Size/leadr_lbbap_sample_size_cip_defib.R

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized using a CONSORT flow diagram similar to that shown in Figure 4. The number of subjects that reach each step will be provided as well as reasons for study exit either between or during steps, including the number of subjects exited for each reason. In addition, compliance to visit windows and enrollment by study site will be summarized.

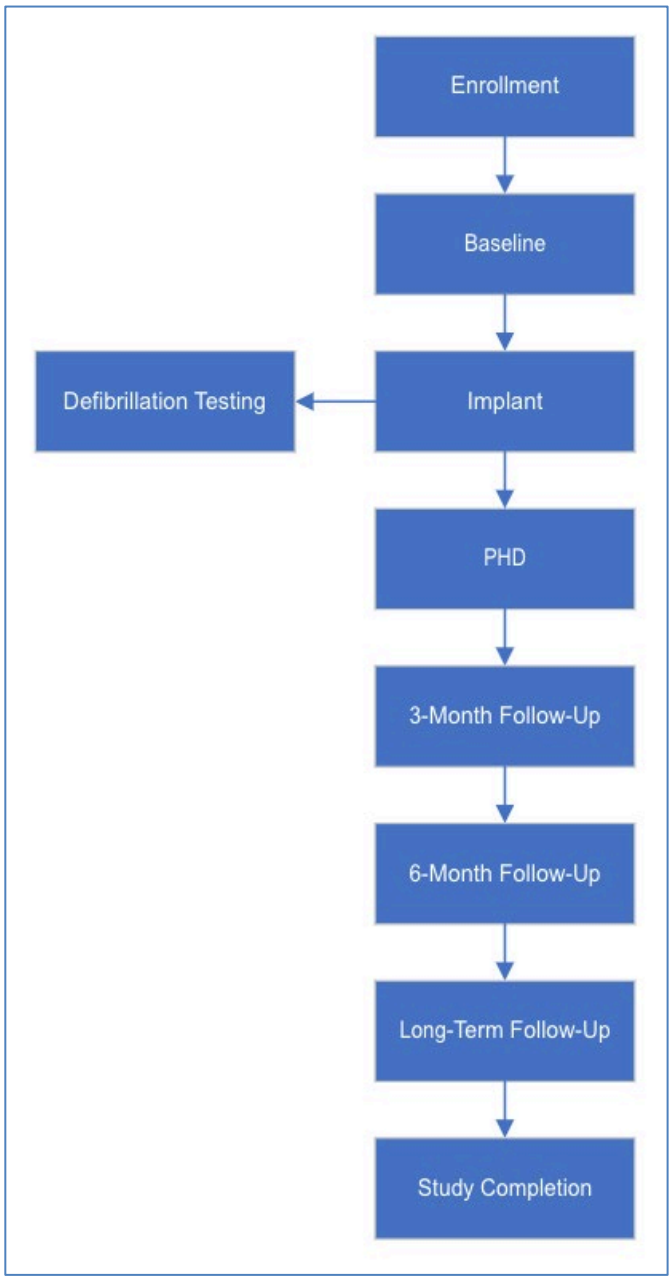


Figure 4. CONSORT flow diagram for summarizing subject disposition.

7.1.2 Clinical Investigation Plan (CIP) Deviations

A frequency table of protocol deviations by deviation type will be created.

On the deviation eCRF study sites will enter "COVID-19" within the answer to the question "What was the reason for the protocol deviation" for COVID-19 pandemic-related deviations. Sites will be trained

and asked to provide sufficient details to clearly describe the situation or the cause of the COVID-19 related deviation.

Inclusion/exclusion violations will not result in subjects being excluded from analysis of objectives. If it is discovered that subjects not meeting the inclusion/exclusion criteria underwent an implant attempt and possibly defibrillation testing, additional analyses may be performed with these subjects excluded.

7.1.3 Analysis Sets

Table 2 defines the main analysis sets to be used in this study. Some additional sets will be defined below for the purpose of supplemental analysis. Details on each use are provided in the relevant section below.

Table 1. Analysis Sets.

Analysis Set Name	Definition	Intended Use
Enrollments	All subjects who signed the informed consent	Baseline summaries Protocol deviation summaries
Implant Attempts	Subjects in the Enrollments set in which an implant of the Next Generation ICD Lead is attempted	Primary Safety Objective Ancillary Implant Success Objective
Intended For Defibrillation Testing	Subjects in the Implant Attempts set in whom the Next Generation ICD Lead is successfully placed at the LBBAP location on or before the cutoff date, which is defined as date on which the 160th subject completes the defibrillation testing protocol in the right order per protocol.	Supplementary analyses for Primary Efficacy Objective
Complete Defibrillation Testing	Subjects in the Intended for Defibrillation Testing set for whom the defibrillation testing protocol was completed in the right order per protocol	Primary Efficacy Objective
Successful LBBAP Implants	Subjects that have a successful Next Generation ICD Lead implant procedure with the Next Generation ICD Lead implanted at the LBBAP location per definitions in section 9.9.2 of the CIP	Ancillary Electrical Performance Objectives (Pacing Threshold, R Wave Sensing, Impedance)* Ancillary ECG Measurement Objective
Successful LBBAP ICD Implants	Subjects in the Successful LBBAP Implants set that are not indicated for CRT	Ancillary KCCQ Objective**
Successful LOT-CRT Implants	Subjects in the Successful LBBAP Implants set that are indicated for CRT and that complete the implant procedure with a successful LV lead implant	Ancillary KCCQ, LVESVi, LVEF Objectives** CCS Objective
Safety	All subjects that sign informed consent	Safety summaries

*Subjects must also have their initially implanted Next Generation ICD Lead still active at the LBBAP location at the 3-month visit and have an available measurement from both implant and 3 months

**Subjects must also have either initially implanted Next Generation ICD Lead or a replacement one still active at the LBBAP location at the 6-month visit

7.2 General Methodology

Data analysis will be performed by Medtronic statisticians or designees.

Hypothesis tests will be conducted at a two-sided alpha level of 0.05 unless otherwise stated.

No adjustment for multiple comparisons is planned.

7.3 Handling of Missing, Unused, and Spurious Data and Dropouts

Instruction on handling missing data as it relates to a specific objective will be described in the section for the objective.

In general, when a date is required for analysis and is only partially available, the following rules will be used:

- If the year or month is missing, the date will be considered completely missing
- If the year and month are provided but the day of the month is missing, it will be initially imputed as the 15th, but may be adjusted if this provides an unrealistic relation to another known date. For example, if the implant date is January 16, and the pre-hospital discharge date is initially imputed as January 15, it may be adjusted to an imputed date of January 17.

7.4 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize subject demographics including age, sex at birth, race, ethnicity as well as other clinical characteristics at baseline. Data for qualitative variables will be presented as incidence rates (total number of subjects, number of events, and percent). Data for continuous variables will be summarized using measures of central tendency and dispersion.

BMI will be calculated as weight in kg/(height in m)^2. Age in years will be calculated by the following formula: date of enrollment, i.e., informed consent date minus date of birth, if date of birth is available. If not, the age in years as indicated on the baseline eCRF will be used.

As described in Table 2, baseline characteristics will be summarized for subjects in the Enrollments set. In addition, these summaries will be provided separately for subjects in the Implant Attempts set and those in the Enrollments set that are not in the Implant Attempts set. The latter group of subjects is expected to be small, so no statistical comparison of these groups is planned. Baseline characteristics will also be summarized for the Complete Defibrillation Testing set.

7.5 Follow-Up Time and Exits

Descriptive statistics will be used to summarize follow-up time, both overall and separately for ICD- and CRT-indicated subjects. A frequency table will be created summarizing the reason for study exit.

7.6 Treatment Characteristics

Procedure time and the number of lead fixation attempts will be summarized both overall and separately for ICD- and CRT-indicated subjects.

7.7 Interim Analyses

The trial will not be stopped early for success or positive results. However, the Data Monitoring Committee may recommend early termination of the study for futility, which does not increase Type I error rates. In order to recommend early termination of the study for efficacy, data contributing to primary efficacy will be evaluated for futility. In addition, other considerations for early stopping for efficacy will include, but are not limited to, the magnitude of effect, primary safety and ancillary objectives, data quality, and consistency of results across subgroups.

Below is a list of the types of anticipated reports to be developed for the study. Other reports not described here may be generated at the request of regulatory authorities and/or for other business purposes if appropriate.

DMC Reports

DMC reports will be developed as needed for DMC meeting. Reporting to the DMC will include an open report available to the steering committee and study team. The open report will include contents that reflects study health and progress. In addition, a closed report may be developed, which would include summaries of data points contributing to the primary safety and efficacy endpoints if requested by the DMC. The closed report would be treated as confidential and only available to members of the DMC and those preparing the closed report. DMC recommendations will be shared with study steering committee and Medtronic management as appropriate.

Clinical Study Reports

Analysis for the LEADR LBBAP study will occur when the first 150 subjects have undergone an implant attempt for LBBAP with the Next Generation defibrillation lead and have had an opportunity to have a 3-month visit, and at least 160 subjects have completed the defibrillation protocol. Analysis will include the primary efficacy and safety objectives. Ancillary objectives will be addressed based on available data.

An additional analysis will be performed once 150 subjects have undergone a LOT-CRT implant attempt for LBBAP with the Next Generation defibrillation lead and have had an opportunity to have a 6-month visit. Analysis will include the primary safety objective and all ancillary objectives, based on available data. The primary efficacy objective will not be updated for this report.

Final Report

A final report will be prepared at study closure. This report will provide updated data summaries, including safety data and ancillary objectives, but inferential analysis for the primary objectives will not be updated.

7.8 Evaluation of Objectives

7.8.1 Primary Objective #1: Efficacy

Demonstrate the percentage of subjects successfully defibrillated at implant with the Next Generation ICD Lead when placed in the LBBAP location exceeds a pre-specified threshold of 88%.

Hypothesis

H_0: The percentage of patients successfully defibrillated at implant with the Next Generation ICD Lead when placed in the LBBAP is ≤88%

H_A: The percentage of patients successfully defibrillated at implant with the Next Generation ICD Lead when placed in the LBBAP does is >88%

Performance Requirement

This objective will be met if the lower bound of the two-sided 95% confidence interval for defibrillation success rate is larger than 88%.

Determination Of Subjects/Data For Analysis

The primary evaluation of this objective will include all subjects in the Complete Defibrillation Testing Protocol set defined in Table 2.

Suggested programming logic:

These subjects can be identified by looking for the set of subjects where the ELEC case report form has YES answered for these questions:

1. Was implant defibrillation testing done
2. Was the lead location LBBAP per CIP acceptance criteria at the start of the defibrillation testing protocol
3. Was any episode successfully induced
4. Was defibrillation testing completed in the right order per protocol

Endpoint Definition

Successful implant defibrillation is defined as achieving any of the following four criteria:

1. First induced SSVA episode successfully terminated with an 18J or maximum output minus 10 Joule (M-10J) shock, or
2. First therapy of the second induced SSVA episode successfully terminated with a M-10J shock, or
3. First therapy after a system reposition of an induced SSVA episode successfully terminated with a M-10J shock, or
4. Two consecutively induced SSVA episodes successfully terminated with a M-10J shock

Figure 5 reproduces a schematic diagram of the defibrillation testing protocol provided in the Clinical Investigation Plan.

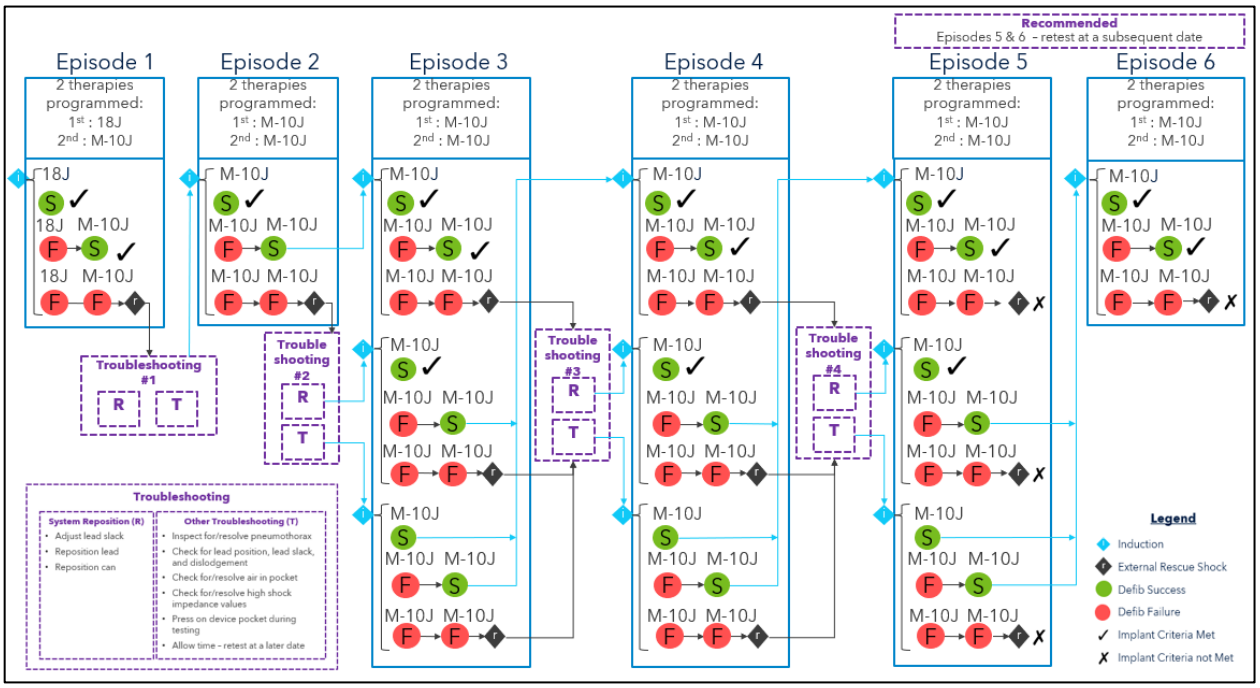


Figure 5. Defibrillation testing protocol.

Suggested programming logic:

Once the set of subjects in the Complete Defibrillation Testing set are identified (covered in the previous subsection), each of these subjects' testing protocols can be assigned as a success or a failure by reviewing data from the ELEC CRF. Records in the corresponding database table will contain these fields, among others:

- System number
- Induced episode number
- Therapy number
- Shock result

Here is an approach that can be used to categorize subjects as successes and failures in a programmatic manner. First, create this derived field in the ELEC CRF table:

- First induced episode for system: Temporarily group records by subject ID and System number, set this field's value to the minimum "Induced episode number" within its group, and then ungroup the records

Next, use if-else or case-when type logic to create a field called "DFT success with one shock" assess the first three criteria for DFT success in this fashion:

1. If there is a DFT record that meets these requirements:
    a. Shock result is either "ICD/CRT-D SHOCK SUCCESSFUL" or "MANUAL ICD/CRT-D SHOCK SUCCESSFUL"
    b. Induced episode number = 1

then set DFT success with one shock = 1

2. Else, if there is a defibrillation testing record that meets these requirements:
    a. Shock result is either "ICD/CRT-D SHOCK SUCCESSFUL" or "MANUAL ICD/CRT-D SHOCK SUCCESSFUL"
    b. Induced episode number = 2
    c. Therapy number = 1

    then set DFT success with one shock = 1
3. Else, if there is a DFT record that meets these requirements:
    a. Shock result is either "ICD/CRT-D SHOCK SUCCESSFUL" or "MANUAL ICD/CRT-D SHOCK SUCCESSFUL"
    b. First induced episode for system = "Induced episode number"
    c. Therapy number = 1

    then set DFT success with one shock = 1. Else, set DFT success with one shock = 0.

Now, to assess the fourth criterion for DFT success, group records by subject ID and Induced episode number, and summarize each group with a single row, creating these summary fields:

- DFT success with one shock = max("DFT success with one shock") = 1
- Any shock success = any Shock result is either "ICD/CRT-D SHOCK SUCCESSFUL" or "MANUAL ICD/CRT-D SHOCK SUCCESSFUL")
- Lagged episode number = "Induced episode number" from prior row
- Lagged shock success = "Any shock success" value from prior row
- Shock success from prior episode =

  ("Induced episode number" – "Lagged episode number" = 1) AND ("Lagged shock success" = TRUE)
- DFT success with two shocks =

  ("Shock success from prior episode" = TRUE) AND ("Any shock success" = TRUE)

Finally, group these summarized records at the subject ID level, and further summarize them with a single field:

- DFT success = any(DFT success with one shock) OR any(DFT success with two shocks)

Analysis Methods

The point estimate of the success rate will be calculated by dividing the number of subjects meeting the endpoint defined in Section 13.4.2 by the number of subjects included in the analysis as defined in Section 13.4.6. A two-sided 95% confidence interval of the defibrillation success rate will be constructed using the exact Binomial method.

Descriptive statistics will also be used to summarize the results, including summaries based on when a patient was successfully defibrillated, i.e. during the first episode, during the second episode, etc.

Suggested programming logic:

Using a table with one row per subject in the Complete Defibrillation Protocol set and containing a column with a success/failure indicator based on the endpoint definition, construct a 95% two-sided confidence interval using the exact Binomial method, also referred to as the Clopper-Pearson method. If the lower bound of this interval is larger than 0.88, the objective is met.

Intercurrent Events and Missing Data

There are multiple reasons (intercurrent events) that subjects in the Intended for Defibrillation Testing set might not complete the testing protocol. Table 3 describes how these cases will be handled.

Table 2: Handling of Intercurrent Events and Missing Data for the Primary Efficacy Objective

Intercurrent Event	Data Collection	Data Analysis
Subject undergoes implant attempt, but a Next Generation ICD Lead is not successfully placed at the LBBAP location	Subject will be followed for 30 days or until resolution of system or procedure-related AEs	Subject is not in intended population for inference
Subject completes the Defibrillation Testing protocol after the cutoff date for the Intended For Defibrillation Testing analysis set	Subject will be followed as per standard protocol	The defibrillation testing protocol is not required for this subject. Data may be included in a descriptive summary, but will not be included in the evaluation of the objective.
No defibrillation testing performed: Despite successfully placing the lead in the LBBAP location before the cutoff date for the Intended For Defibrillation Testing set, the implanter does not begin defibrillation testing	Subject will be followed and data collected after intercurrent event	Subject is in intended population for inference but cannot be included in main analysis of objective (principal stratum strategy). Therefore, subject will be included in tipping point analysis of defibrillation success rate, and in poolability analysis to characterize outcomes during follow-up
Incomplete defibrillation testing data: Despite successfully placing the lead in the LBBAP location before the cutoff date for the Intended For Defibrillation Testing set, implanter either does not complete testing in the right order per protocol or the Next Generation ICD Lead does not remain at the LBBAP location throughout the protocol	Subject will be followed and data collected after intercurrent event	Subject is in intended population for inference but cannot be included in main analysis of objective (principal stratum strategy). Therefore, subject will be included in tipping point analysis of defibrillation success rate, and in poolability analysis to characterize outcomes during follow-up

A two-dimensional tipping point analysis will be used to understand the sensitivity of the results to using the principal stratum strategy and excluding subjects with no defibrillation testing performed or with incomplete defibrillation data. This approach will explore the combination of success/failure outcomes across the range of these two types of subjects where the primary efficacy objective would be met or not met.

Poolability

In poolability assessments, defibrillation efficacy will be estimated separately for:

1. indication: ICD vs CRT
2. sex at birth: male vs female subjects
3. age groups: for example, splitting subjects into those with age at implant in the interval 12-18, 19-65, and 65+
4. geographic region: US/Canada subjects vs those in other geographies

In each case, a logistic regression will be used to test the null hypothesis that the poolability factor has no association with defibrillation testing success probability at a significance level of 0.05. The number and specificity of subgroups defined for each factor may depend on data availability.

Additionally, the defibrillation success probability will be estimated separately for each investigational site with at least five subjects, and a graphical summary of these estimates relative to the overall rate will be provided, for example in a forest plot. More evaluation may be carried out in the event that the poolability factor p-value is less than 0.05 and subgroup success probability point estimate is lower than expected.

7.8.2 Primary Objective #2: Safety

Estimate the Next Generation ICD Lead-related major complication rate at 3-months post implant when the Next Generation ICD Lead implant is attempted in the LBBAP location. This objective does not involve testing a hypothesis, and does not have a pre-specified performance requirement.

Determination Of Subjects/Data For Analysis

All subjects attempting an implant with the Next Generation ICD Lead in the LBBAP location (the Implant Attempts analysis set) will be included.

Some subjects may undergo a procedure to replace the Next Generation ICD Lead within 30 days of the initial implant. The initial implants for these subjects will be included. However, the replacement procedure will not be included in the main analysis of this objective. Instead, they will be considered in a supplementary analysis described in the Intercurrent Events and Missing Data subsection below.

Suggested programming logic:

All subjects that have an Implant CRF completed where it is indicated that a Next Generation ICD Lead implant attempt was performed, except only include the first implant for subjects with a replacement procedure.

Endpoint definition

For an adverse event (AE) to meet the endpoint, defined as a subject's first occurrence of a major complication related to the Next Generation ICD Lead, as determined by an independent Clinical Events Committee (CEC), the event must have occurred within 90 days (inclusive) of the Next Generation ICD Lead implant attempt and be adjudicated by the CEC as being a major complication related (causal relationship) to the Next Generation ICD Lead. Major complications are those complications resulting in:

- Death
- Hospitalization (in-patient)
- Lead Fracture
- Prolongation of an existing hospitalization by at least 48 hours
- System Revision (reposition, replacement, explant)

To clarify, in order for a hospitalization to classify a complication as major, it must be a new hospitalization or a prolongation by at least 48 hours.

Analysis Methods

The point estimate for the complication rate will be based on a Kaplan-Meier curve, generated using each subject's time to first Next Generation ICD Lead-related major complication or time to last exposure to the Next Generation ICD Lead if a subject does not have a major complication, in which case the subject will be censored.

Last exposure to the Next Generation ICD Lead will be defined as the date of their pre-hospital discharge visit, last follow-up visit (including remote visits), study exit date (if exited for reason other than lost-to-follow-up), or date of death, whichever is last. Additionally, if a subject has an explant of the Next Generation ICD Lead that is not related to a Next Generation ICD Lead major complication the subject will have their last exposure date set to their explant date.

Results will also be summarized in aggregate using descriptive statistics, including the total number of major complications experienced by subjects for whom an implant is attempted. Kaplan-Meier curve estimates will be provided for follow-up time points past 3 months based on availability of data if number at risk is greater than 30.

Suggested programming logic:

Here is logic that can be used to conduct the main analysis for this objective:

- Create a table with one row per subject, containing these fields
    - Event indicator = 1 if the subject has any AEs meeting the endpoint definition (restricting attention to the first implant if the subject had a replacement procedure)

  - Time to event = number of days elapsed from implant to the onset of the first of these AEs if there are any, missing otherwise
  - Date of last exposure = latest of:
    - Pre-hospital discharge visit date
    - Last follow-up visit date, including remote visits
    - Study exit date, ignoring exit forms where the reason for exit is not "LOST TO FOLLOW-UP"
    - Date of death
  - Time to last exposure = number of days elapsed from implant to date of last exposure
  - Survival time = time to event if event indicator = 1, time to last exposure otherwise
- Estimate the survival curve based on the survival time and event indicator defined here, using the Kaplan-Meier estimator and Greenwood formula for variance to calculate a point estimate and 95% confidence interval
- Obtain major complication rate (i.e. the cumulative probability of a major complication) point estimate and 95% confidence interval by subtracting the survival point estimate and confidence interval bounds from 1

Intercurrent Events and Missing Data

There are multiple reasons (intercurrent events) that subjects in the Implant Attempts set might not remain in the study until the 3 month visit. The analysis method used here inherently accounts for these cases, but Table 4 clarifies how several of them will be handled.

Table 3: Handling of Intercurrent Events and Missing Data for the Primary Safety Objective

Intercurrent Event	Data Collection	Data Analysis
Subject undergoes implant attempt with the Next Generation ICD Lead, but it is not successfully placed at the LBBAP location, and no major complication related to the Next Generation ICD Lead occurs	Subject will be followed for 30 days or until or until all procedure or system related AEs are resolved, whichever occurs later	Subject enters analysis with event indicator = 0 and survival time = 0, which is equivalent to not being included in analysis
Subject has a major complication related to the Next Generation ICD Lead during the implant procedure (regardless of whether implant is successful)	Standard follow-up rules from CIP apply	Subject enters analysis with event indicator = 1 and survival time = 1
Subject undergoes successful implant attempt, and is lost to follow-up after hospital discharge with no additional follow-up	Subject exited after at least two documented unsuccessful contact attempts	Subject's last exposure will be the date of their pre-hospital discharge, and standard rules for determining time to event (if any) apply
Subject undergoes a replacement procedure for the Next Generation ICD Lead	Standard follow-up rules from CIP apply	Subject's replacement lead will be included in a supplementary analysis in which both initial and replacement leads are included in a survival analysis used to estimated complication rate. A robust variance technique may be used to acknowledge possible correlation within subject.

Poolability

In poolability assessments, the major complication rate will be estimated separately for:

1. sex: male vs female subjects
2. age groups: for example, splitting subjects into those with age at implant in the interval 12-18, 19-65, or 65+
3. geographic region: US/Canada subjects vs those in other geographies
4. indication: ICD vs CRT

In each case, a Cox proportional hazards regression may be used to test the null hypothesis that the poolability factor has a hazard ratio of 1 at a significance level of 0.05. The number and specificity of subgroups will depend on data availability.

Additionally, the 90-day complication rate will be estimated separately for each investigational site with at least five subjects, and a graphical summary of these estimates relative to the overall rate will be provided, for example in a forest plot. More evaluation may be carried out in the event that the poolability factor p-value is less than 0.05.

7.8.3 Ancillary Objectives

The following ancillary objectives are descriptive in nature and are intended to gain additional information about the Next Generation ICD Lead. There are no formal statistical hypotheses tested for the ancillary objectives. There will be no data imputations for missingness unless specified otherwise.

[redacted]

Analysis Methods

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.9 Safety Evaluation

All reportable adverse events will be collected throughout the study duration, starting at the time of signing the ICF. For purposes of reporting, events shall be captured on an AE eCRF.

An independent CEC will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related, and all events resulting in death, to determine relatedness and complication (major, minor) or observation classifications.

If available, the CEC adjudication will be used for reporting. If the CEC adjudication is not available (e.g. interim reports), the investigator classification will be used. If there is a disagreement between the CEC and the investigator, this disagreement will be reported in terms of AE listings/death listings, however the CEC's classification will be used for analysis purposes.

Results will be summarized using descriptive statistics. Number of events, number and percentages of subjects experiencing system and/or procedure-related adverse events will be reported, as well as, in the case of system-related events, the specific component of the system to which the event was related to describe adverse device effects. The seriousness of adverse events and type of event (complication/observation) will also be summarized as well as whether events were unanticipated adverse device effects or unanticipated serious adverse device effects. Details of individual adverse events including MedDRA key term, actions, outcome, relatedness and seriousness will be listed.

The prevalence of adverse events will further be summarized by MedDRA (Medical Dictionary for Regulatory Activities) key term. The Preferred Term (PT) term will be used. The number of events and the number of subjects and the percentage of subjects with an event will be summarized per each PT Term.

The independent CEC will also review deaths, and classify them based on cardiac relatedness (cardiac death, sudden cardiac-death, etc). A listing of deaths will be provided with these classifications. All subject deaths must be reported by the investigator to Medtronic on an AE eCRF (AE with fatal outcome).

Additionally, any device deficiencies related to the Next Generation ICD lead or accessories will be collected. Device deficiency information will be collected throughout the study and reported to Medtronic. The term and center description of individual device deficiencies and whether they could have led to a serious adverse device effect will be reported in a listing.

Adverse events, deaths, and device deficiencies will be summarized for the Safety cohort.

7.10 Changes to Planned Analysis

In Section 13.6.9 of the CIP, it states that subjects whose initially implanted Next Generation ICD Lead is no longer active at the 6-month visit will be excluded from the analysis of Ancillary Objective #9 (CCS). However, as stated in Section 7.10.6 of this SAP, all subjects with a successful LOT-CRT implant will be included in the analysis of Ancillary Objective #9.

8. Validation Requirements

The main analyses for the primary efficacy and safety objectives will be validated at Level I. Other objectives and analysis output will be validated at level II.

Level I validation refers to independent programming in which an internal Medtronic statistician will write code independently of the original analysis code and results from the two programs will be compared to confirm matching results. It is the intent that Level I validation will be completed between two assigned study statisticians.

Level II validation refers to peer review, in which an internal Medtronic statistician or statistical programmer will review code written to create analysis output or, where appropriate, will perform manual calculations or simple programming checks to verify the output

Level III validation (self-validation) may be appropriate for minor updates to tables/figures when a validated program is revised for cosmetic changes.